UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,674	07/20/2001	Donald S. Karanewsky	480140.444C1	6380

500 7590 03/07/2006

SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 03/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/912,674	KARANEWSKY, DONALD S.	
	Examiner	Art Unit	
	David Lukton	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 12/19/05, claims 1-40, 45-50 have been cancelled, and claims 41-44 amended.

Claims 41-44 are now pending; the pending claims are examined in this Office action.

✦

35 U.S.C. §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 44 is rejected under 35 USC §101 because the claimed invention is not supported by a well established utility.

Claim 44 is drawn to a method of "preventing" ischemic injury. This term implies that if one of the claimed compounds were administered to each of 1000 patients who were about to suffer an ischemic event, that not a single one of those patients would exhibit any evidence (e.g., histological) or symptoms of ischemic damage. That would be impressive enough, if it could be achieved. But the claim goes further. The claim encompasses the possibility that if the compound was administered several hours or even weeks after the ischemic insult, that no damage of any kind would occur, i.e., that the damage could be reversed, and that it would be fully reversed in all 1000 patients. Clearly, applicants haven't even taken a small step in the direction of showing any of this.

In addition, Read S. J. (*Drugs and Aging* 14 (1) 11-39, 1999) discloses that effective treatments for limiting the neurological damage after stroke have proven elusive.

[This particular ground of rejection can be overcome by deleting the term "preventing" from the claim].

Claim 44 is also rejected under 35 USC §112 first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-44 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown (table 3, pages 63-65) that the claimed compounds can inhibit one or more caspases. Based on this, applicants are asserting the claimed compounds can be used to treat any of several diseases including (page 31, line 17+; page 32., line 3+) the following: septic shock, septicemia, and adult respiratory distress syndrome, rheumatoid arthritis, SLE, scleroderma, chronic thyroiditis, Graves' disease,

autoimmune gastritis, insulin-dependent diabetes mellitus, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, Alzheimer's disease, Parkinson's disease, primary lateral sclerosis, myocardial infarction, stroke, ischemic kidney disease, multiple sclerosis, and amyotrophic lateral sclerosis.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Consider the following:

- Frost Robert A. (*American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **283** (3) R698-709, 2002) investigated the regulation of TNFα and IL-6 by lipopolysaccharide (LPS) in C2C12 myoblasts and mouse skeletal muscle. Treatment of myocytes with IL-1 or TNF-alpha also increased IL-6 mRNA content, and the increase in IL-6 mRNA due to LPS could not be prevented by pretreatment with antagonists to either IL -1 or TNF. Thus, even if applicants could successfully block all interleukin-1 production using the claimed compounds, interleukin-6 levels could not be controlled, thereby leading to "unpredictable" results on inflammatory response.

- Meyers K. P. (*Inflammation* **17** (2) 121-34, 1993) discloses that interleukin-1 receptor antagonist was not active as an anti-inflammatory agent in the 24-h pleurisy model (carageenan-induced pleurisy).

- Rosenbaum J. T. (*Archives of Ophthalmology* **110** (4) 547-9, 1992) discloses that interleukin-1 receptor antagonist did not produce significant reduction in inflammation subsequent to an active Arthus reaction or subsequent to the

intravitreal injection of 125 ng of endotoxin. Rosenbaum suggests that the failure of IL-1RA to be therapeutically effective may be due in part to the presence of other pro-inflammatory cytokines.

- Brennan (*Clinical and Experimental Immunology* **81**, 278-85, 1990) discloses that TGF-β was effective to inhibit IL-1β production in LPs-stimulated peripheral blood mononuclear cells, but only if the cells were pretreated with TGF-β. The IL-1β production was not inhibited if the TGF-β was applied after the inducing stimulus. The point here is that if a scientist has evidence that a given agent "X" is effective to inhibit production of IL-1β when used prior to stimulation of cells (which stimulation produces the IL-1β), attempting to inhibit production of IL-1β by using agent "X" after stimulation of the cells leads to "unpredictable" results.

- Paris (*Journal of Infectious Diseases* **171**, 161-69, 1995) discloses that IL-1RA was not effective to treat inflammation caused by gram-negative bacteria.

With respect to treatment of ischemia and stroke, Read S. J. (*Drugs and Aging* **14** (1) 11-39, 1999) discloses (e.g., abstract) that although many drugs are effective in animal models of cerebral ischemia, these drugs have largely failed to fulfill their promise in clinical trials. Jonas (*Annals NY Acad Sci* 939, 257-67, 2001) discloses that, to the extent that therapeutic efficacy has been achieved in the treatment of ischemia, success could only be achieved if the drug in question was administered within three hours of the ischemic event. The instant claims encompass administration of the compound several days after the ischemia has occurred.

Thus, attempting to extrapolate from *in vitro* ICE inhibition to treatment of inflammatory disease leads to "unpredictable" results; undue experimentation would be required to practice the claimed invention.

In response to the foregoing, applicants have pointed to Ku (*Cytokine* **8**, 377, 1996) which provides evidence that there exists an ICE inhibitor which is effective to treat arthritis in mice. Perhaps there is a case to be made that the compounds (to which the instant claims are directed) will be effective to treat arthritis. However, there is no claim drawn to such. In any case, applicants have argued that because arthritis is an inflammatory disease, it therefor follows that all inflammatory diseases can be treated by any ICE inhibitor. However, the logic is flawed. Consider the following three statements:

1. Dogs are often observed to engage in barking
2. All dogs are mammals
3. Therefore, it must be true that all mammals are prone to barking.

Presumably, applicants will recognize that the third statement does not follow from the first two. However, this is exactly the logic that applicants are employing. As indicated above, applicants have argued that because arthritis is an inflammatory disease, it therefore follows that all inflammatory and autoimmune diseases can be treated by any ICE inhibitor. Consider that autoimmune diseases include the following:

> Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis, pernicious anemia, autoimmune atrophic gastritis, Addison's disease, premature menopause, insulin dependent diabetes mellitus, Goodpasture's syndrome, myasthenia gravis, male infertility, pemphigus vulgaris, pemphigoid, sympathetic opthalmia, phacogenic uveitis, multiple sclerosis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis, cryptogenic cirrhosis, ulcerative colitis, Sjogren's syndrome, rheumatoid arthritis, dermatomyositis, scleroderma, mixed connective tissue disease, discoid lupus erythematosis, systemic lupus erythematosus

Clearly, the mere proposition that arthritis can be successfully treated does not mean that any of the foregoing can be successfully treated.

Applicants have also pointed to Thornberry (*Science* **281**, 1312, 1998) which offers speculation as to what might happen at some point in the future. In that article, it is stated that caspases are "potential targets" for the treatment of certain inflammatory disorders. The examiner does not argue that for all time points in the future, attempts to treat inflammatory diseases using apoptosis inhibitors will invariably lead to failure. What the examiner argues, instead, is that as of October of 1999, the evidence supports the proposition that attempts to treat inflammatory disease (and the other diseases recited in the claims) will produce "unpredictable" results. Furthermore, applicants own assertion regarding apoptosis actually supports the conclusion that the patients' condition will worsen. Consider the following:

- Kanegane Hirokazu (*Pediatric nephrology* (Berlin, Germany) **18** (5) 454-6, 2003) discloses that mutations in the *Fas* gene result in impaired apoptosis (at least *Fas*-mediated apoptosis), and that as a result of this, autoimmune disease and glomerulonephritis occurs. Thus, one would conclude that inhibiting apoptosis will result in autoimmune disease and glomerulonephritis.

- Strasser A. (*Annals of the New York Academy of Sciences* **917**, 541-8, 2000) discloses that Bim is a member of the Bcl-2 family of proteins, and that Bim

induces apoptosis. Strasser further discloses that Bim-deficient mice develop autoimmune disease and glomerulonephritis. Thus, one would conclude that inhibiting apoptosis will result in autoimmune disease and glomerulonephritis.

- Van Den Brande, Jan M. H. (*Annals of the New York Academy of Sciences* **973** 166-80, 2002) discloses that Crohn's disease can be treated by inducing T-lymphocyte apoptosis. The skilled artisan would conclude that if Crohn's disease can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Kacinski B M (*Annals of the New York Academy of Sciences* **941**, 194-9, 2001 discloses that the methods of treating cutaneous T-cell lymphoma that are most successful act by inducing T-cell apoptosis. The skilled artisan would therefor conclude that if cutaneous T-cell lymphoma can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Tsuchiyama Y (*Kidney International* **58** (5) 1941-52, 2000) discloses that galectin-9 is effective to treat nephritis, and that dexamethasone is also effective in this regard. Both of these agents induced apoptosis of splenic CD8+ cells. The skilled artisan would conclude that if nephritis can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Li X. C. (*Current Opinion in Immunology* **12** (5) 522-7, 2000) discloses that T cell apoptosis is required for transplantation tolerance. The skilled immunologist would conclude that attempts to inhibit apoptosis would result in transplantation rejection.

- Bednarski Jeffrey J. (*Arthritis and rheumatism* **48** (3) 757-66, 2003) discloses that a compound designated Bz-423 induces apoptosis, and is effective to mitigate autoimmune disease such as glomerulonephritis and arthritis. The skilled immunologist would conclude that attempts to inhibit apoptosis would cause autoimmune disease, or at least exacerbate it.

Thus, there is evidence to suggest that administering the compounds (to which the

instant claims are directed) to a patient suffering from an inflammatory condition will only serve to exacerbate the patient's condition. Under such circumstances, one certainly cannot "predict" therapeutic efficacy.

Accordingly, "undue experimentation" will be required to practice the claimed invention.

✦

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at (571)272-0974. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON, PH.D.
PRIMARY EXAMINER